

REMARKS/ARGUMENTS

Support for the Amendments

The amendment to claim 2 is an incorporation of the recitations of claim 1, from which claim 2 originally depended, to render claim 2 independent, and the reduction of the definition of X to the phosphoryl group (optionally substituted) shown prominently in various parts of the specification, including the examples. The remaining amendments are conforming amendments to render the remaining claims consistent with the amendment to claim 2. No new matter is presented.

Claim Rejections - 35 USC § 102

The rejection of claims 1-29, 33-35, 37, 38, 41, 42, 46, and 47 as anticipated by Winchell et al. US 5,874,573 is respectfully traversed. While the '573 patent discloses pharmaceutical compositions containing chelators associated in various ways with metal cations, the only specific mention of calcium or magnesium appears in the last sentence of the last paragraph at column 10, lines 56-62, which states

“The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.”

and the listing of two calcium complexes and two magnesium complexes at column 68, lines 6-16. The sentence quoted above from column 10 does not describe complexes of calcium with the chelators but instead merely pharmaceutical compositions that include calcium chloride in admixture with the chelators to form calcium salts when the chelators contain acid groups, as

“pH adjusting and buffering agents, etc.” The four complexes listed in column 68 are not covered by the claims of the present application as amended above. Since Applicant’s complexes are not explicitly disclosed, anticipation of Applicant’s claims is not present.

Also, as discussed below, the key feature of the present invention is the unexpected improvement in biological activity of chelators when administered as complexes with dicationic metals (such as calcium and magnesium) rather than monocationic metals (such as sodium). Nothing in the ’573 patent suggests that such unexpected improvement would occur.

Claim Rejections - 35 USC § 103

The rejection of claims 1-50 as obvious over Winchell et al. US 5,874,573 in view of Weglicki US 5,854,287 is likewise respectfully traversed. A key feature of the present invention is the unexpected improvement in biological activity of chelators when administered as complexes with dicationic metals (such as calcium and magnesium) rather than monocationic metals (such as sodium). This improvement is expressly demonstrated by Applicant’s own experimental data as presented in Example 7, pages 89-91 of the present application. In the tests reported in this example, sodium, magnesium, and calcium complexes of N,N’,N’-tri(dihydroxyphosphoryl methyl)-1,4,7-triazacyclononane were separately administered to hearts of male Wistar rats at various concentrations prior to the onset of induced ischemia. As the example itself reports on page 91 of the specification:

“To summarize, after 15 minutes of ischemia followed by reperfusion, the trisodium complex produced no beneficial result, while the monomagnesium, monosodium complex and monocalcium, monosodium complex produced multiple significant benefits. The beneficial results obtained with the monocalcium, monosodium complex involved more functional parameters and were observed at lower concentrations and over a wider range of concentrations than were observed with the monomagnesium, monosodium complex.”

Thus, the complex of the chelator with calcium and sodium and the complex of the chelator with magnesium and sodium were both superior in performance to the complex with sodium only, and the complex that contained calcium demonstrated an additional improvement over the complex that contained magnesium. This is a distinct improvement that is not suggested by any part of the disclosure in the Winchell reference.

The Weglicki reference discloses that certain compounds unrelated in structure to those of the present invention or to those of Winchell et al. '573 have antioxidant activity. Applicant does not deny that certain antioxidants are known to have certain therapeutic activities, but this in itself does not mean that every compound with antioxidant activity will be effective in all of the same disease conditions, including the disease conditions that are recited in Applicant's claims, or even that a supposed common antioxidant activity itself is enough to link two disclosures that address two such different classes of molecular structures. Still further, and perhaps even most critical, is the failure of Weglicki to suggest that any particular subset of the class of compounds disclosed in Winchell '573 is any more effective than any other subset. Neither of the two references discloses or suggests this anomaly. Accordingly, the present invention is not obvious over the disclosures of these two references, either individually or in combination.

Double Patenting

The rejection of claims 1-26 Winchell et al. US 5,874,573 for double patenting is likewise respectfully traversed. As noted above, a key feature of the present invention is the unexpected improvement in biological activity of chelators when administered as complexes with dicationic metals (such as calcium and magnesium) rather than monocationic metals (such as sodium). The complexes with dicationic metals are a subset of the larger class claimed by Winchell '573, and are indeed patentably distinct, as Applicant's experimental data attests. The artisan would have no way of knowing that complexes with dicationic metals would have any special benefit and would not be motivated to select these over any other complexes in the

Winchell '573 class. Accordingly, the present claims are not obvious over those of Winchell '573.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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